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(21) International Application Number: PCT/US99/10357 (22) International Filing Date: 12 May 1999 (12.05.99) (30) Priority Data: 60/085,394 14 May 1998 (14.05.98) US (71) Applicant: DU PONT PHARMACEUTICALS COMPANY [US/US]; 974 Centre Road, WR-1ST18, Wilmington, DE 19807 (US). (72) Inventors: VOSS, Matthew, E.; 106 Westview Drive, Lincoln University, PA 19352 (US). DECICCO, Carl, P.; 17 Ridgewood Turn, Newark, DE 19711 (US). WEXLER, Ruth, R.; 2205 Patwynn Road, Wilmington, DE 19810 (US). (74) Agent: VANCE, David, H.; Du Pont Pharmaceuticals Com- pany, Legal Patent Records Center, 1007 Market Street, Wilmington, DE 19898 (US).		(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.
(54) Title: NOVEL SUBSTITUTED ARYL HYDROXAMIC ACIDS AS METALLOPROTEINASE INHIBITORS (57) Abstract <p>The present application describes novel substituted aryl hydroxamic acids of formula (I) or pharmaceutically acceptable salt forms thereof, wherein ring A is a 5-8 membered ring containing from 0-1 additional heteroatoms selected from N, O, and S, which are useful as metalloproteinase inhibitors and inhibitors of TNF.</p> <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>		

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TITLENOVEL SUBSTITUTED ARYL HYDROXAMIC ACIDS AS METALLOPROTEINASE
INHIBITORS

5

FIELD OF THE INVENTION

This invention relates generally to novel substituted
aryl hydroxamic acid derivatives as metalloproteinase
inhibitors, and inhibitors of TNF, pharmaceutical compositions
10 containing the same, and methods of using the same.

BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteinases
(MP) are important in the uncontrolled breakdown of connective
15 tissue, including proteoglycan and collagen, leading to
resorption of the extracellular matrix. In addition
metalloproteinases have been shown to be involved in the
processing of cell surface proteins that have been implicated
in a number of diseases, including inflammatory disorders.

20 Tumor necrosis factor alpha (TNF- α) is a cell associated
cytokine that is processed from a 26kd precursor form to a
17kd active form. TNF- α has been shown to be a primary
mediator in humans and in animals, of inflammation, fever, and
acute phase responses, similar to those observed during acute
25 infection and shock. Excess TNF- α has been shown to be
lethal. There is now considerable evidence that blocking the
effects of TNF- α with specific antibodies can be beneficial in
a variety of circumstances including autoimmune diseases such
as rheumatoid arthritis (Feldman et al, Lancet, 1994, 344,
30 1105) and non-insulin dependent diabetes melitus. (Lohmander
L.S. et al. Arthritis Rheum. 36, 1993, 1214-22) and Crohn's
disease (MacDonald T. et al. Clin. Exp. Immunol. 81, 1990,
301).

Compounds which inhibit the production of TNF- α are
35 therefore of therapeutic importance for the treatment of
inflammatory disorders. Recently it has been shown that a
matrix metalloproteinase (MMP) or family of
metalloproteinases, hereafter known as TNF-convertases (TNF-

C), as well as other MP's are capable of cleaving TNF- α from its cell associated to soluble form (Gearing et al Nature, 1994, 370, 555). This invention describes molecules that inhibit this conversion and hence the secretion of active TNF- α from cells.

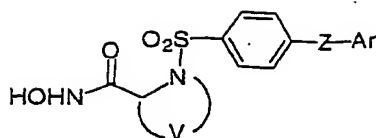
The compounds of the current invention inhibit the production of TNF- α from cells stimulated with LPS. Furthermore, some of the present compounds are selective for TNF-C inhibition over matrix metalloproteinases. This selectivity offers a distinct advancement over compounds of the current art, because non-selective MMP inhibitors have been found to produce toxic manifestations related to tendonitis and fibroplasia in clinical trials.

The compounds of the current invention do not inhibit MMPs at concentrations expected to produce a therapeutically positive response through the inhibition of TNF. The compounds of the present invention are therefore expected to be safer to patients taking the drug because of their selective inhibition profile for soluble TNF- α production.

The present novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock, haemodynamic shock, sepsis syndrom, post ischaemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, neuro-denerative diseases and non-insulin dependent diabetes melitus.

Since excessive TNF- α production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF- α production may also have a particular advantage in diseases where both mechanisms are involved.

WO 97/20824 describes MMP inhibitors of formula A:



A

wherein ring V contains six atoms, Z is O or S, and Ar is an aryl or heteroaryl group. Ar is preferably a monocyclic aryl group with an optional para substituent or an unsubstituted monocyclic heteroaryl group. WO 97/20824 does not disclose any compounds wherein Ar is a disubstituted phenyl or pyridyl or a bicyclic heteroaryl group.

The compounds of the current invention act as inhibitors of MPs, that process TNF- α . These novel molecules are provided as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of TNF-C, and other metalloproteinases by molecules of the present invention indicates they are anti-inflammatory.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel substituted aryl hydroxamic acids which are useful as metalloprotease inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

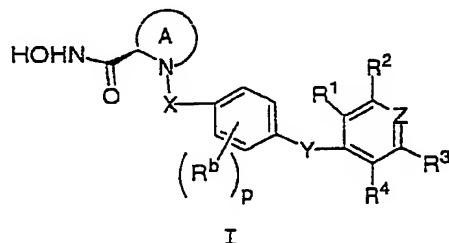
It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating inflammatory disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide novel compounds for use in therapy.

It is another object of the present invention to provide the use of novel compounds for the manufacture of a medicament for the treatment of a disease related to metalloproteases.

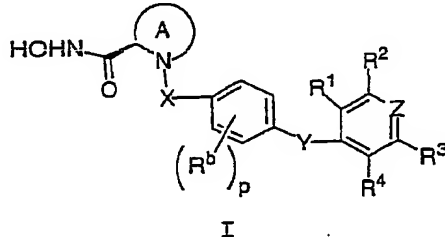
These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):



or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, p, X, Y, Z, R^b, R¹, R², R³, and R⁴ are defined below, are effective metalloprotease inhibitors with unique and specific inhibitory properties for TNF.

15 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

ring A is a 5-8 membered heterocyclic ring containing 0-1 additional heteroatoms selected from the group: O, NH, S, SO, and SO₂, and substituted with 0-3 R^a;

R^a, at each occurrence, is independently selected from the group: =O, CH₃, CH₂CH₃, CF₃, Cl, F, OH, OCH₃, and OCF₃;

R^b , at each occurrence, is independently F or CH_3 ;

X is selected from the group: CH_2 , $C(O)$, $C(O)O$, $C(O)NH$, $S(O)$,
5 $S(O)_2$, $S(O)NH$, and $S(O)_2NH$;

Y is selected from the group: $(CH_2)_n$, OCH_2 , CH_2O , $OCH(CH_3)$,
 $CH(CH_3)O$, $OC(CH_3)_2$, $C(CH_3)_2O$, OCF_2 , CF_2O , $S(O)_pCH_2$,
10 $CH_2S(O)_p$, NH , $NHCH_2$, and CH_2NH ;

Z is CH or N;

R^1 is selected from the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 ,
 $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

15 R^2 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 ,
 $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

R^3 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 ,
20 $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

provided that when Z is N, R^2 and R^3 are other than F, Br, or
I;

25 R^4 is H;

alternatively, R^3 and R^4 are taken together with the carbon
atoms to which they are attached to form a 5-6 membered
aromatic ring containing 0-2 heteroatoms selected from
30 the group: O, S, NH, and N and substituted with 0-2 R^c ;

R^c is selected from the group: H, F, Cl, Br, I, NO_2 , CH_3 ,
 CH_2CH_3 , $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

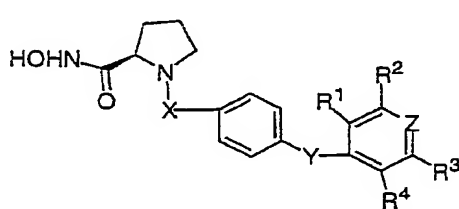
35 when R^3 and R^4 are taken together, then R^2 is selected from
the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, OCH_3 ,
 OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

n is selected from the group: 1, 2, and 3; and,

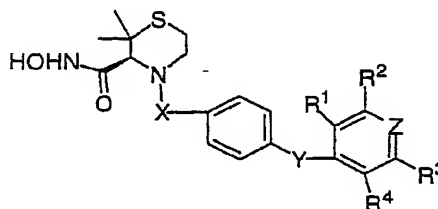
p is selected from the group: 0, 1, and 2.

5

[2] In a preferred embodiment, the present invention provides a compound of formula Ia or Ib:



Ia



Ib

wherein, X is selected from the group: CH₂, C(O), C(O)O, C(O)NH, S(O), S(O)₂, S(O)NH, and S(O)₂NH;

Y is selected from the group: CH₂, (CH₂)₂, OCH₂, CH₂O, NH, NHCH₂, and CH₂NH;

Z is CH or N;

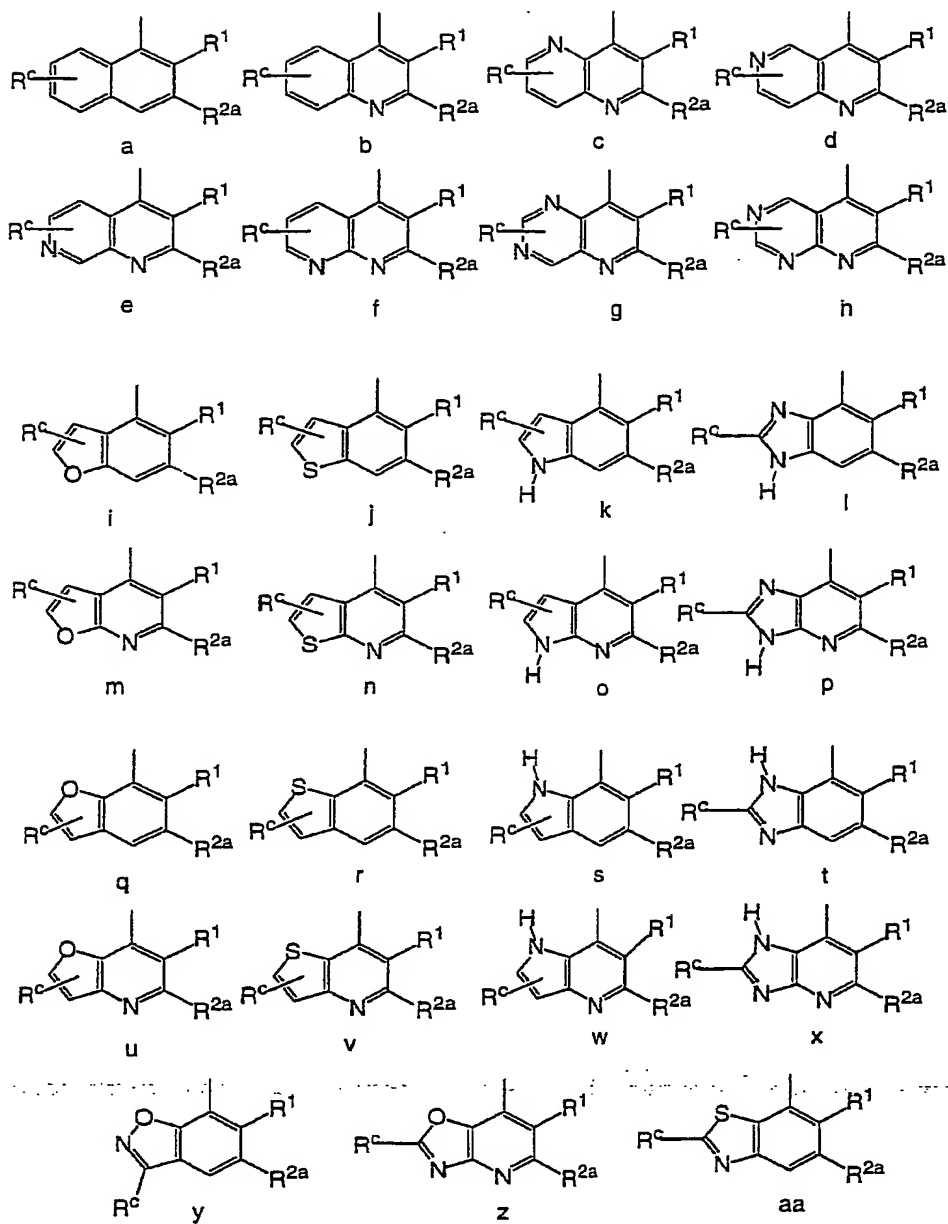
R¹ is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R² is selected from the group: F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R³ is selected from the group: F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R⁴ is H;

alternatively, R³ and R⁴ are taken together with the aromatic ring to which they are attached to form an aromatic ring selected from a-aa:



R^c is selected from the group: H, F, Cl, Br, I, NO_2 , CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;
and,

R^{2a} is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃.

5 [3] In an even further preferred embodiment, the present invention provides novel compounds selected from:

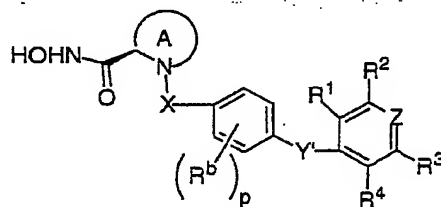
- 10 (S)-4-[[4-[(3,5-dimethylphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 15 (S)-4-[[4-[(3,5-ditrifluoromethylphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(3,5-dibromophenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 20 (S)-4-[[4-[(3,5-diethoxyphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(3,5-dichlorophenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 25 (S)-4-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 30 (S)-4-[[4-[(2,6-dimethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 35 (S)-4-[[4-[(2,6-diethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(2,6-ditrifluoromethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 40 (S)-4-[[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 45 (S)-N-hydroxy-2,2-dimethyl-4-[[4-(4-quinolinylmethoxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 50 (S)-N-hydroxy-2,2-dimethyl-4-[[4-(2-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;

- (S) -N-hydroxy-2,2-dimethyl-4-[[[4-(2-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 5 (S) -N-hydroxy-2,2-dimethyl-4-[[[4-(2-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 10 (S) -N-hydroxy-2,2-dimethyl-4-[[[4-(2-ethoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 15 (S) -N-hydroxy-2,2-dimethyl-4-[[[4-(2-trifluoromethyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 1-[[4-[(3,5-dimethylphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 20 1-[[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(3,5-ditrifluoromethylphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 25 1-[[4-[(3,5-dibromophenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(3,5-diethoxyphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 30 1-[[4-[(3,5-dichlorophenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 35 1-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(2,6-dimethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 40 1-[[4-[(2,6-diethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(2,6-ditrifluoromethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 45 1-[[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 50 1-[[4-(4-quinolinylmethoxy)phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 55 1-[[[4-(2-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;

- 1-[[[4-(2-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 5 1-[[[4-(2-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-(2-ethoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 10 1-[[[4-(2-trifluoromethyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 15 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(3-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(3-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 20 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(3-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 25 1-[[[4-(3-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[[4-(3-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide; and,
- 30 1-[[[4-(3-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 35 or a pharmaceutically acceptable salt form thereof.

[4] In a second embodiment, the present invention provides a novel compound of formula II:

40



II

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

45

ring A is a 5-8 membered heterocyclic ring containing 0-1 additional heteroatoms selected from the group: O, NH, S, SO, and SO₂, and substituted with 0-3 R^a;

- 5 R^a, at each occurrence, is independently selected from the group: =O, CH₃, CH₂CH₃, CF₃, Cl, F, OH, OCH₃, and OCF₃;

R^b, at each occurrence, is independently F or CH₃;

- 10 X is selected from the group: CH₂, C(O), C(O)O, C(O)NH, S(O), S(O)₂, S(O)NH, and S(O)₂NH;

Y' is S or O;

- 15 Z is CH or N;

R¹ is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

- 20 R² is selected from the group: F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R³ is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

- 25 provided that when Z is N, R² and R³ are other than F, Br, or I;

R⁴ is H;

- 30

alternatively, R³ and R⁴ are taken together with the carbon atoms to which they are attached to form a 5-6 membered aromatic ring containing 0-2 heteroatoms selected from the group: O, S, NH, and N and substituted with 0-1 R^c;

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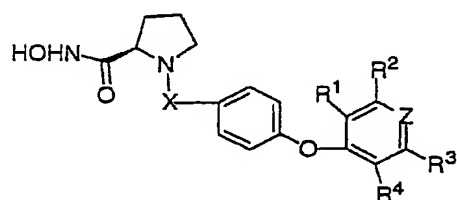
R^c is selected from the group: H, F, Cl, Br, I, NO₂, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

when R^3 and R^4 are taken together, then R^2 is selected from the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

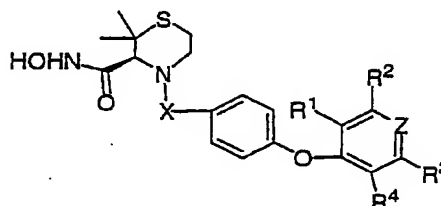
5 n is selected from 1, 2, and 3; and,

p is selected from 0, 1, and 2.

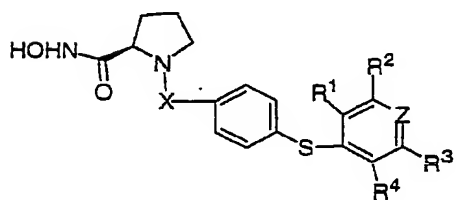
10 [5] In a preferred embodiment, the present invention provides a compound of formula IIa, IIb, IIc or IIId:



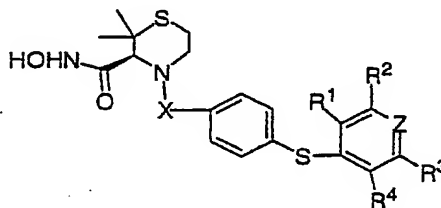
IIa



IIb



IIc



IIId

wherein, X is selected from the group: CH_2 , $C(O)$, $C(O)O$,
 20 $C(O)NH$, $S(O)$, $S(O)_2$, $S(O)NH$, and $S(O)_2NH$;

Z is CH or N;

R^1 is H or F;

25

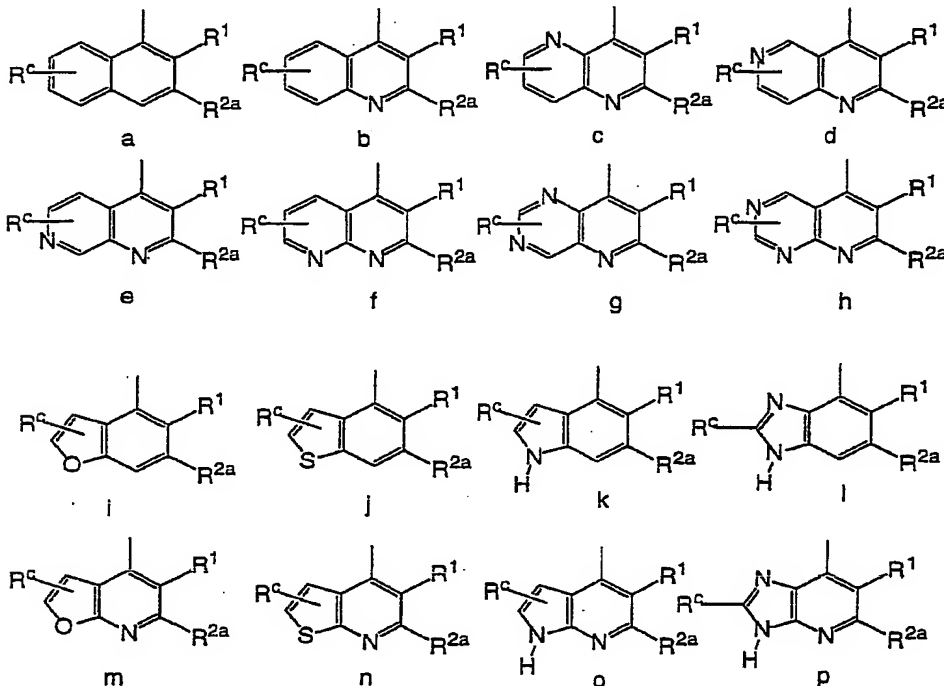
R^2 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 ,
 $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

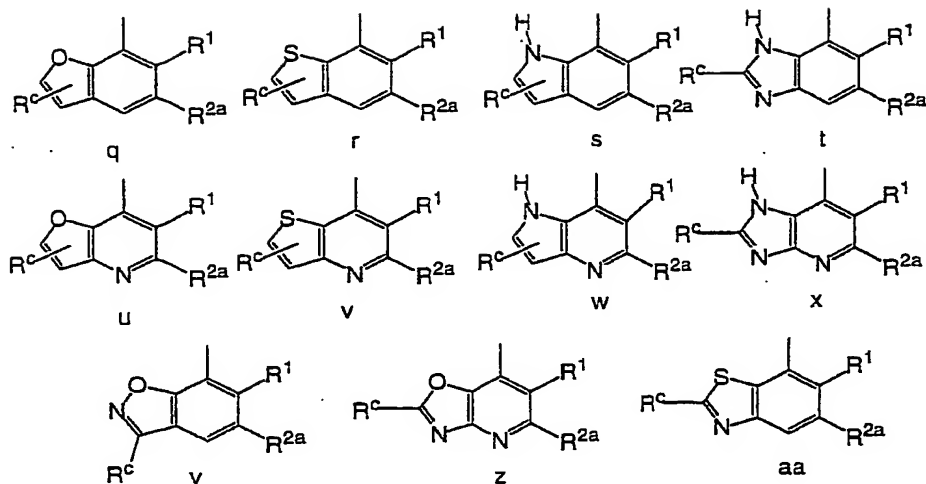
R^3 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

R^4 is H;

5

alternatively, R^3 and R^4 are taken together with the aromatic ring to which they are attached to form an aromatic ring selected from a-aa:





R^c is selected from the group: H, F, Cl, Br, I, NO_2 , CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;
 5 and,

R^{2a} is selected from the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 .

10

In a third embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or (II) or a
 15 pharmaceutically acceptable salt form thereof.

In a fourth embodiment, the present invention provides a novel method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of
 20 formula (I) or (II) or a pharmaceutically acceptable salt form thereof.

In a fifth embodiment, the present invention provides a novel method of treating a condition or disease mediated by
 25 MMPs, TNF, aggrecanase, or a combination thereof in a mammal,

comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or (II) or a pharmaceutically acceptable salt form thereof.

5

In a sixth embodiment, the present invention provides a novel method of reducing levels of TNF in patients without inhibiting MMPs, comprising: MMP-1, MMP-2, and MMP-9, and reduce the potential of side effects mediated by these enzymes comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or (II) or a pharmaceutically acceptable salt form thereof.

15 In a seventh embodiment, the present invention provides a novel method of treating a condition or disease wherein the disease or condition is referred to as rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, multiple sclerosis, neurodegenerative diseases, psoriasis, 20 autoimmune disease, Crohn's disease, inflammatory bowel disease, or HIV infection in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or (II) or a pharmaceutically acceptable salt form thereof.

25

In a eighth embodiment, the present invention provides a novel method of treating a condition or disease wherein the disease or condition is referred to as fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia, 30 alcoholism, acute phase response, acute infection, shock; graft versus host reaction, solid tumor growth and tumor invasion by secondary metastases, or neovascular glaucoma, in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a 35 compound of formula (I) or (II) or a pharmaceutically acceptable salt form thereof.

An ninth embodiment of the invention provides novel preferred compounds that are orally bioavailable and selective for the inhibition of TNF- α through its convertase(s), over enzymes of the matrix metalloproteinase class.

In a tenth embodiment, the present invention provides a novel compound of formula (I) or (II) for use in therapy.

In an eleventh embodiment, the present invention provides the use of a novel compound of formula (I) or (II) for the manufacture of a medicament for the treatment of a disease related to metalloproteases.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced.

The present invention includes all isotopes of atoms occurring in the present compounds. Isotopes include those

atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

5 When any variable (e.g., R^b) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R^6 , then said group may optionally be
10 substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

 When a bond to a substituent is shown to cross a bond
15 connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such
20 substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

 As used herein, "C₁₋₆ alkyl" or "C₁₋₆ alkylene" is intended to include both branched and straight-chain saturated
25 aliphatic hydrocarbon groups having the specified number of carbon atoms, examples of which include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, pentyl, and hexyl; "Alkenyl" or
 "alkenylene" is intended to include hydrocarbon chains of
30 either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl, propenyl, and the like. "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either a straight or branched
35 configuration and one or more carbon-carbon triple bonds which may occur in any stable point along the chain, such as ethynyl, propynyl, and the like.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

5 As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, 10 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

15 As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 8- membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and 20 from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached 25 to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically

noted, a nitrogen in the heterocycle may optionally be 30 quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic 35 heterocyclic system" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group

consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to,

5 1H-indazole, 2-pyrrolidinyl, 2H,6H-1,5,2-dithiazinyl, 2H-pyrrolyl, 3H-indolyl, 4-piperidinyl, 4aH-carbazole, 4H-quinolizinyl, 6H-1,2,5-thiadiazinyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl,

10 benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalonyl, carbazolyl, 4aH-carbazolyl, b-carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl,

15 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl,

20 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinylperimidinyl, phenanthridinyl, phenanthrolinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, piperidinyl, 4-piperidinyl, piperonyl, pteridinyl,

25 purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, quinazoliny, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, carbolinyl,

30 tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl,

35 triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl,

oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazoliny, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

5 The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity,
10 irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

 As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent
15 compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The
20 pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as
25 hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic,
30 sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

 The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which
35 contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water

or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

30

SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited

herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section.

5 The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of
10 solvent, reaction atmosphere, reaction temperature, duration of the experiment and work up procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality
15 present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

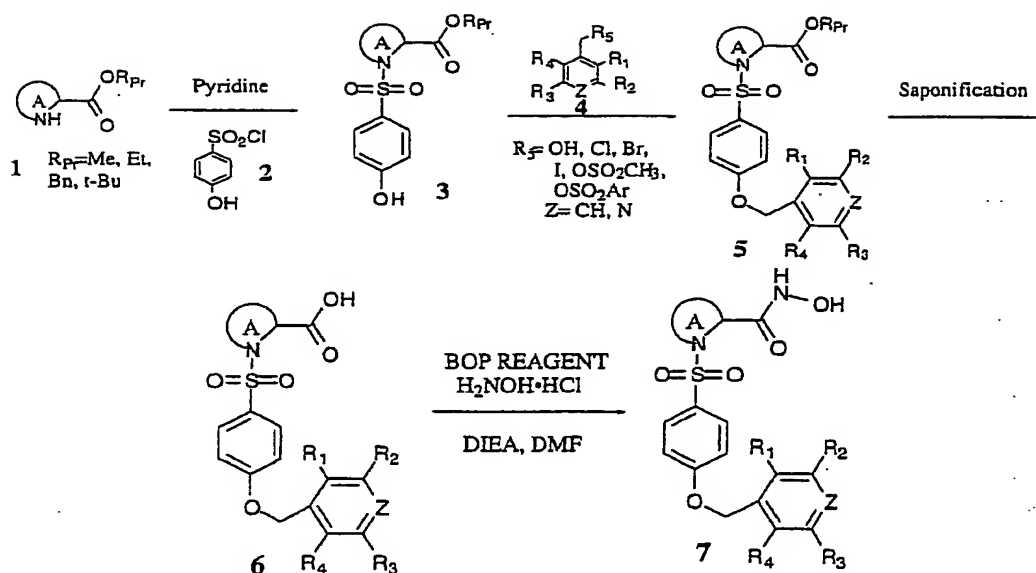
20 A series of 4-substituted aryl sulfonamides of formula 7 are described in Scheme 1. A suitable cyclic amino ester scaffold (1) was treated with 4-hydroxybenzenesulfonyl chloride (2, R.W. Campbell, H.W. Hill, Jr. *J. Org. Chem.*, 1975, 38, 1047) to provide hydroxy aryl sulfonamide 3.

25 Coupling of 3 to 4 can be accomplished by Mitsunobu reaction (DEAD, TEA, R₅=OH) or by formation of the alkaline salt of 3, by treatment with an alkaline carbonate in a polar aprotic solvent, then reaction with 4 (R₅=Cl, Br, I, OSO₂CH₃, OSO₂Ar)

30 to give biaryl sulfonamide 5. Saponification of the ester could be accomplished by acidic (6N HCl reflux) or basic conditions (LiOH, THF:H₂O) to afford carboxylic acid 6 which could be converted to the hydroxamic acid under a variety of conditions with the preferred being BOP reagent, DIEA, and hydroxylamine hydrochloride.

35

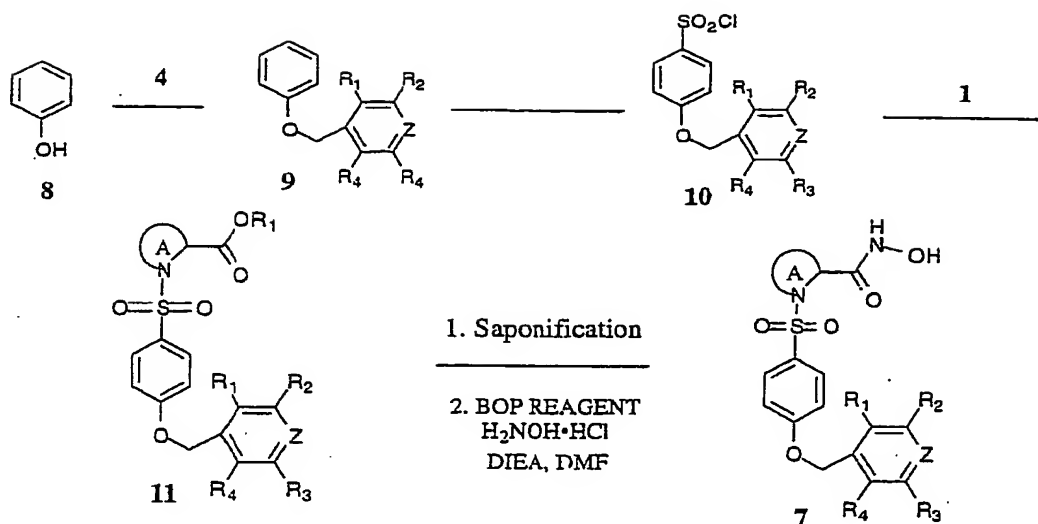
Scheme 1:



5

Another synthetic sequence for the synthesis of 7 constructs the biarylsulfonamide portion and then couples it to scaffold 1 (Scheme 2). Starting with phenol 8, 4 was attached using the same Mitsunobu or alkylation conditions previously described in Scheme 1 to provide the alkylated phenol 9. In this scheme, 4 was chosen with the proviso that it must allow regioselective chlorosulfonylation on the phenol ring of 9 in sufficient yield to continue the synthetic sequence. Useful conditions for conversion of 9 to 10 are chlorosulfonic acid in an appropriate solvent at an appropriate temperature. An alternative synthesis was to begin the sequence with 4-bromophenol then append the chlorosulfonyl group on by a metallation, sulfuryl chloride quench sequence. Reaction of scaffold 1 with sulfonyl chloride 10 then gave intermediate 5 which can be converted to 7 by the conditions previously discussed in Scheme 1.

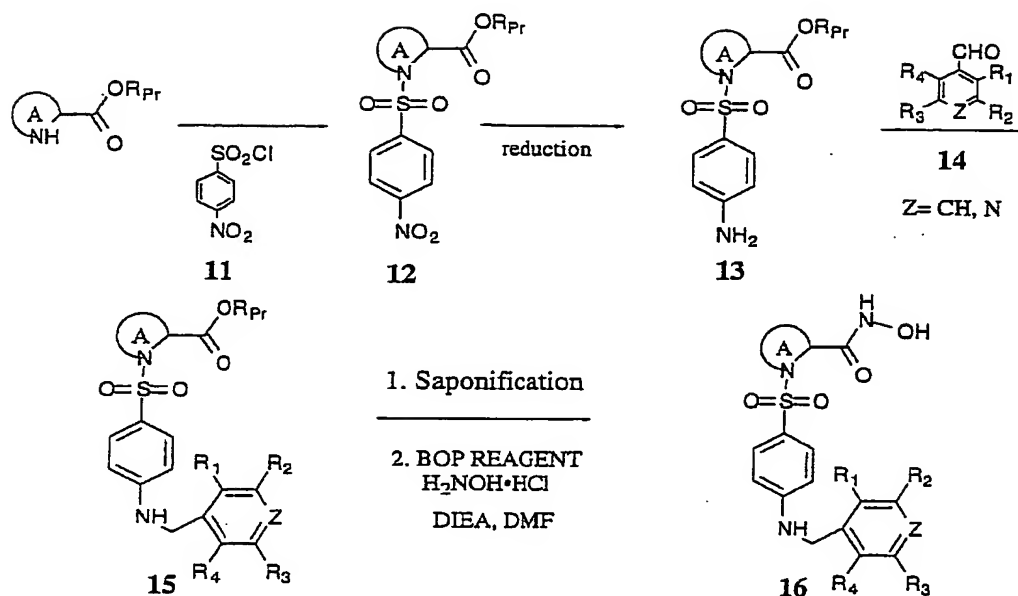
Scheme 2



5

- Synthesis of 16 with an aminomethyl attachment between the aryl groups in the sulfonamide side chain can be accomplished by the sequence outlined in Scheme 3. Scaffold 1 was reacted with 4-nitrobenzenesulfonyl chloride to provide 12.
- 10 The nitro group was then reduced to afford amine 14. Substitution of the nitrogen can be accomplished by treatment of 13 with aldehyde 14 under reductive alkylation conditions (sodium cyanoborohydride, methanol being typical) to give biaryl sulfonamide 15. The ester 15 was then converted to
- 15 the hydroxamate 16 by standard conditions.

Scheme 3

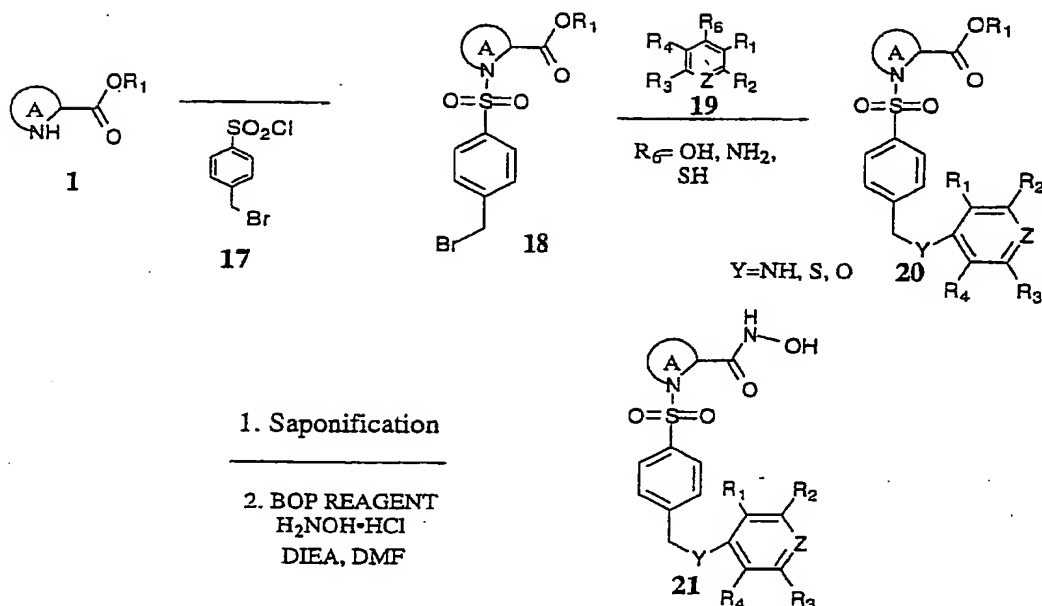


5

Synthesis of hydroxamate 21 where the connection between the benzenesulfonamide and the other aromatic group is CH_2NH , CH_2O , or CH_2S is outlined in Scheme 4. Scaffold 1 was reacted with 4-bromomethylbenzenesulfonyl chloride to give aryl sulfonamide 18. Displacement of the bromide could be accomplished with aryl or heteroaryl amines, alcohols or thiols to provide 20. The ester 20 was then converted to the hydroxamate 21 under the conditions previously discussed.

10

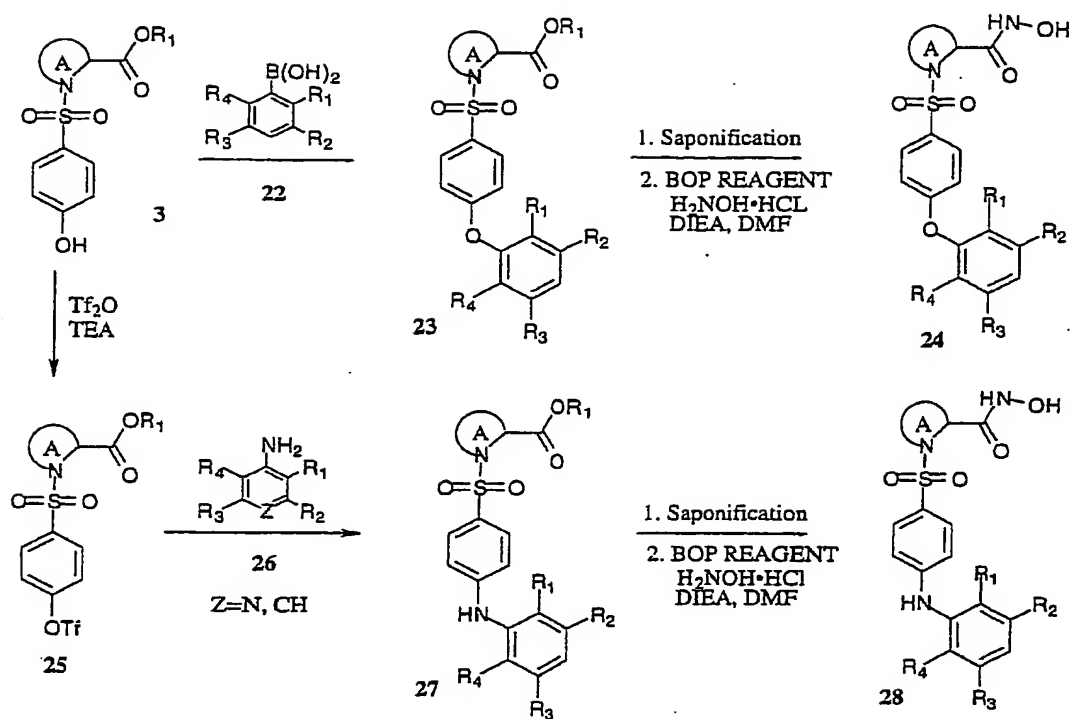
Scheme 4



5

The biaryl ether and biaryl amine analogs 23 and 25 can be prepared from 4-hydroxybenzenesulfonamide 3 according to the procedures outlined in Scheme 5. The biaryl ether analogs are prepared directly from 3 by treatment with an aryl boronic acid in the presence of cupric acetate and amine base (Chan, D.M.T.; Winters, M.P.; Monaco, K.L.; Wang, R. 35th Nat. Organic Symposium, San Antonio, TX, June 24, 1997, Abstract M92) to give 22 which was then converted to hydroxamate 23. Biaryl amines are synthesized from 3 by first synthesis of triflate 24 (Tf₂O, TEA) then coupling with aryl amines 25 (Louie, J.; Driver, M.S.; Hamann, B.C.; Hartig, J. F. *J. Org. Chem.* 1997, 62(5), 1268-73, Wolfe, J.P.; Buchwald, S.L. *J. Org. Chem.* 1997, 62(5), 1264-67) provide biaryl aminesulfonamide 25 which is converted to the hydroxamate 26 under the usual conditions.

Scheme 5

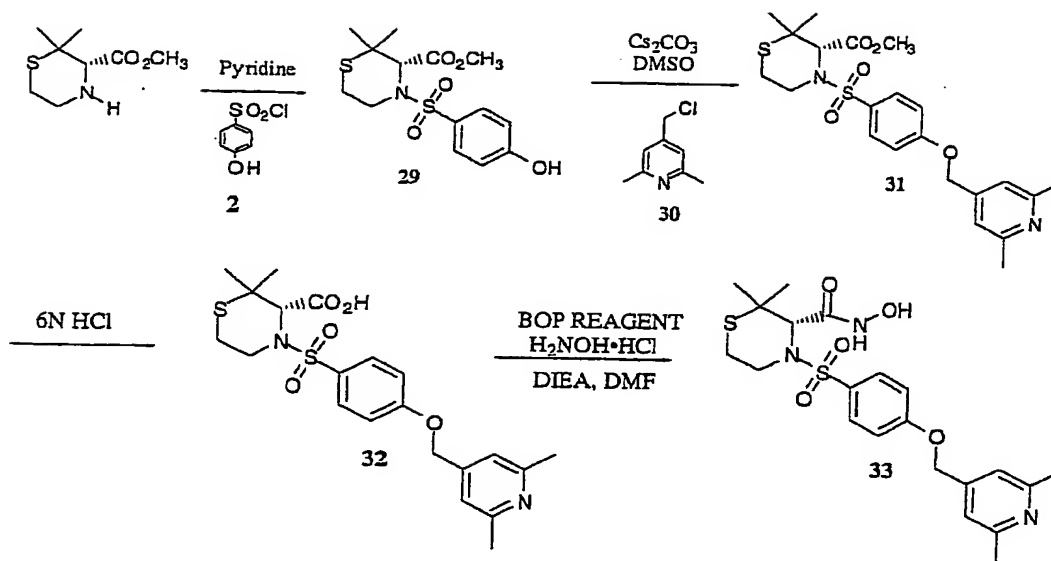


5

An example of the synthesis of a preferred 3-thiomorpholine scaffold is given in Scheme 6. Thiomorpholine 29 was reacted with 4-hydroxybenzenesulfonyl chloride in pyridine to give hydroxysulfonamide 30. Alkylation with cesium carbonate and 4-chloromethyl-2,6-dimethylpyridine hydrochloride afforded ether sulfonamide 31 in good yield. Saponification was accomplished with 6N HCl under reflux for 15h then treatment with BOP reagent, DIEA, and hydroxylamine hydrochloride provided the hydroxamate 33.

15

Scheme 6



5

One diastereomer of a compound of Formula I may display superior activity compared with the others. When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotherapy*, 1995, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* 1995, 36, 8937-8940).

15

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

20

Examples

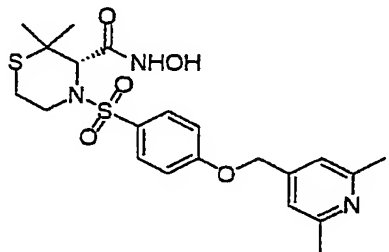
Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, " ^1H " for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz"

25

for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

(S)-4-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide

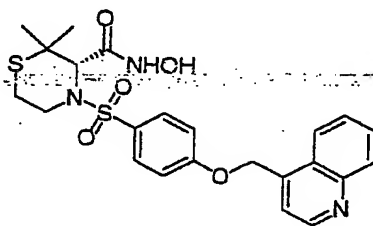


1a: 4-Hydroxybenzenesulfonyl chloride (0.41g, 0.22 mmol) in methylene chloride (1 mL) was added dropwise to 3(S)-methyl-2,2-dimethyl-thiomorpholinecarboxylate (0.37 g, 0.20 mmol) in pyridine (4 mL) at room temperature. The reaction was stirred for 30 min then the solvent was removed *in vacuo* and the residue taken up in ethyl acetate: water (1:1, 20 mL). The mixture was extracted with ethyl acetate (3x) and the combined extracts were washed with 10% citric acid (2 x 25 mL), water (25 mL), and brine (25 mL), dried over MgSO_4 , and the solvent removed *in vacuo*. The residue was purified by flash chromatography (SiO_2 , 50% ethyl acetate:hexane) to provided 1a (249 mg, 37%) as a light yellow solid. MS(ESI-pos) m/e 406 (M+H)⁺.

1b: Cesium carbonate (396 mg, 1.22 mmol) was added in one portion to 1a (140 mg, 0.41 mmol), sodium iodide (79 mg, 0.53 mmol), and 4-chloromethyl-2,6-dimethylpyridine hydrochloride (101 mg, 0.53 mmol) in anhydrous DMSO (4 mL) at room temperature. The reaction was stirred for 2.5 h then diluted with water (15 mL) and extracted with ethyl acetate (3 x 15

1d: Diisopropyl ethyl amine (440 mg, 3.4 mmol) was added dropwise to 1c (0.34 mmol), BOP reagent (165 mg, 0.37 mmol). and hydroxylamine hydrochloride (71 mg, 1.02 mmol) in DMF (3 mL) at room temperature. The reaction was stirred overnight and the solvent removed in vacuo. The reaction mixture was purified by reverse phase HPLC (acetonitrile:water) to (S)-4-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide (65 mg, 33%) as a fluffy white powder after lyophilization. MS(ESI-pos) m/e 466 (M+H)⁺.

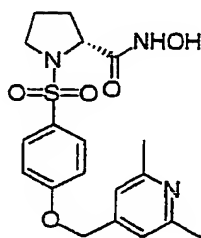
25 (S)-N-hydroxy-2,2-dimethyl-4-[[4-(4-quinolinylmethoxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide



30

Example 3

[N-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]]-D-proline-N-hydroxyamide



5

3a: The procedure used was analogous to procedure 1a.
MS(ESI-pos) m/e 308 (M+Na)⁺.

10 3b: The procedure used was analogous to procedure 1b.
MS(ESI-pos) m/e 405 (M+H)⁺.

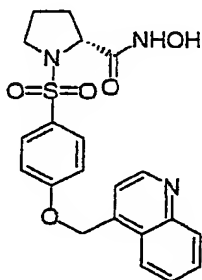
3c: Lithium Hydroxide (30 mg, 0.71 mmol) in water (1 mL) was added to 1b in THF (3 mL) at room temperature. The reaction was stirred 3 h then the solvent was evaporated. The residue was taken up in water (10 mL) and washed with ether (2x). The ether layer was discarded and the aqueous layer acidified with 1N HCl (1.5 mL). The solvent was removed *in vacuo* and the residue was dried by evaporation *in vacuo* with toluene (3x).
15 The crude carboxylic acid 3c was taken forward without addition purification. MS(ESI-neg) m/e 389 (M-H)⁻.
20

3d: The procedure used was analogous to procedure 1d.
MS(ESI-pos) m/e 406 (M+H)⁺.

25

Example 4

[N-[[4-(4-quinolinylmethoxy)phenyl]sulfonyl]]-D-proline-N-hydroxyamide



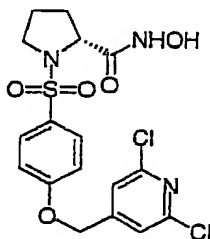
5

Example 4 was produce analogously to example 3 with the substitution of 4-chloromethylquinoline for 4-chloromethyl-2,6-dimethylpyridine. MS(ESI-pos) m/e 428 (M+H)⁺.

10

Example 5

[N-[[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]sulfonyl]]-D-proline-N-hydroxyamide



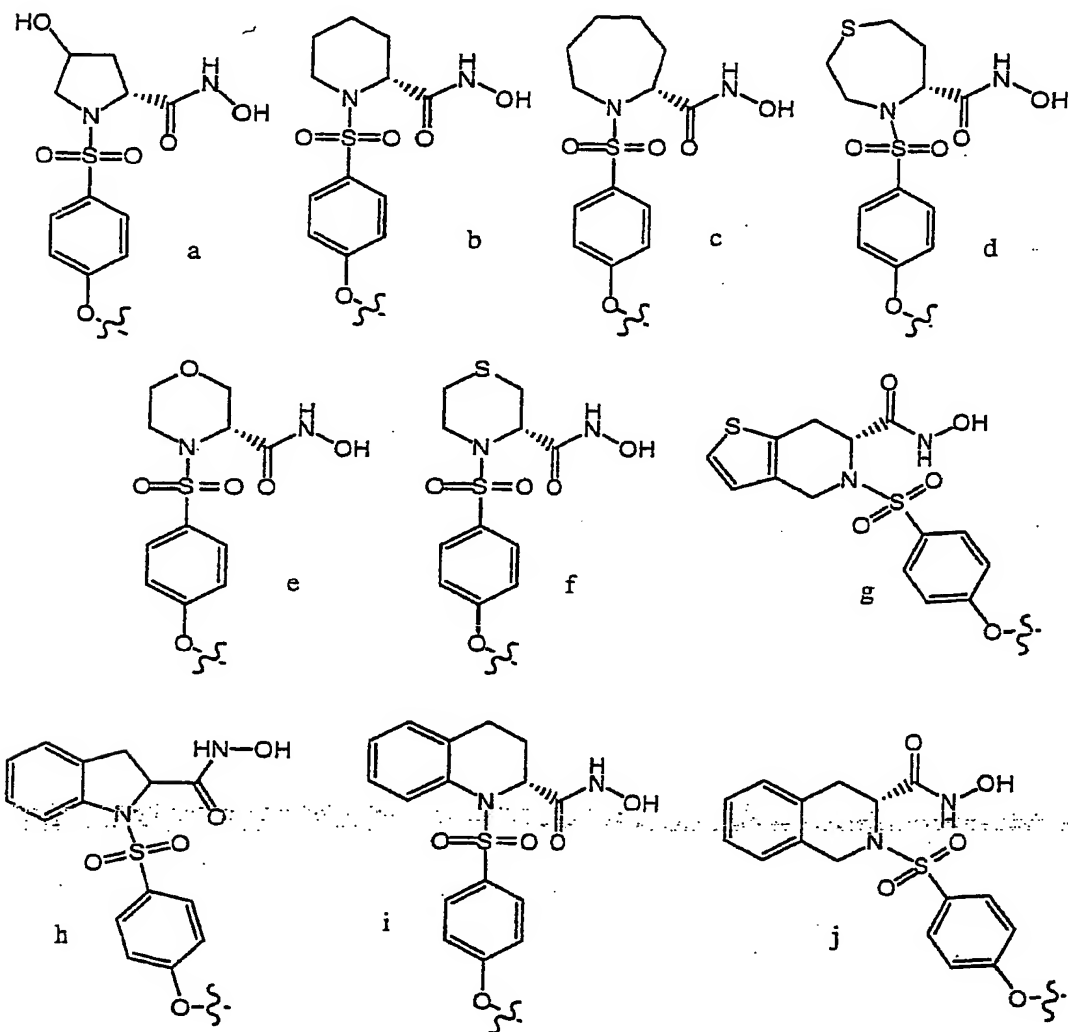
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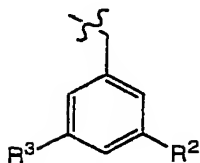
Example 5 was produce analogously to example 3 with the substitution of 4-bromomethyl-2,6-dichloropyridine for 4-chloromethyl-2,6-dimethylpyridine. MS(ESI-neg) m/e 444 and 446 (M-H)⁻.

20

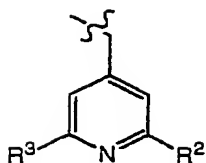
The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formula at the start of the table. For example, in Table 1, example 1 is intended to be paired with each of formulae a-i.

Table 1

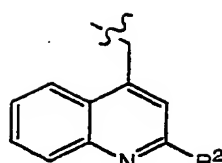




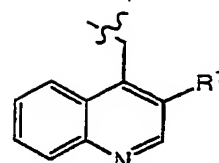
A



B



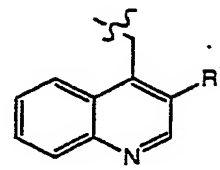
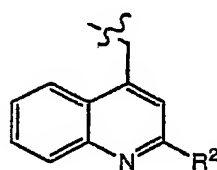
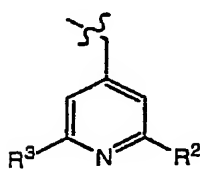
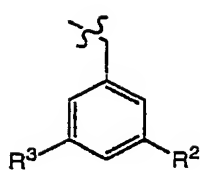
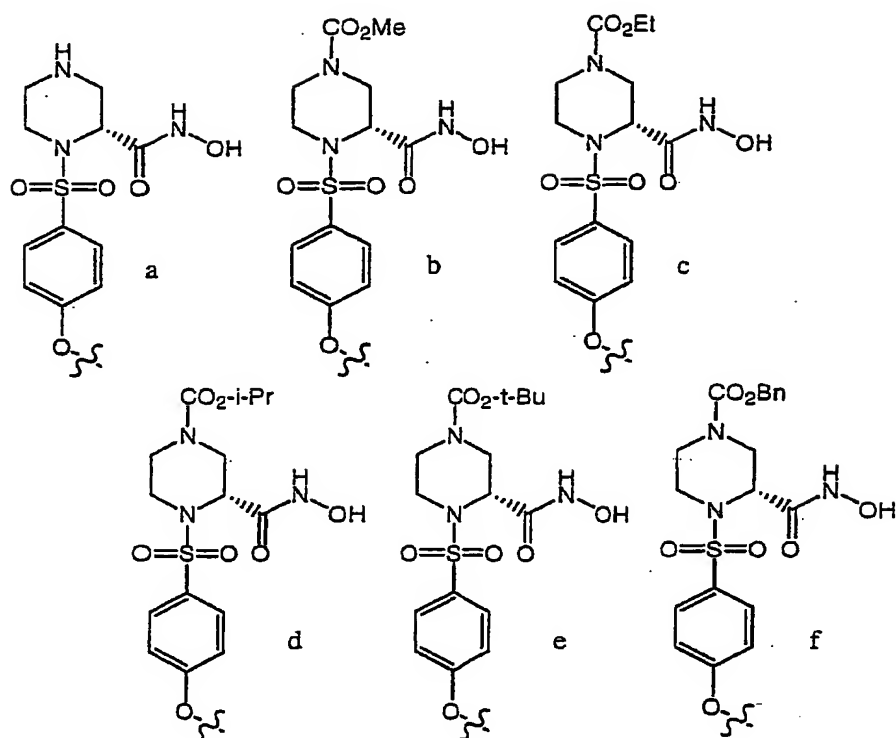
C



D

Ex #	Core	R ²	R ³	R ¹
1	A	CH ₃	CH ₃	-
2	A	OCH ₃	OCH ₃	-
3	A	CF ₃	CF ₃	-
4	A	OCH ₂ CH ₃	OCH ₂ CH ₃	-
5	A	OCH(CH ₃) ₂	OCH(CH ₃) ₂	-
6	A	Cl	Cl	-
7	A	Br	Br	-
8	B	CH ₃	CH ₃	-
9	B	OCH ₃	OCH ₃	-
10	B	OCH ₂ CH ₃	OCH ₂ CH ₃	-
11	B	OCH(CH ₃) ₂	OCH(CH ₃) ₂	-
12	B	Cl	Cl	-
13	C	H	-	-
14	C	CH ₃	-	-
15	C	OCH ₃	-	-
16	C	OCH ₂ CH ₃	-	-
17	C	OCH(CH ₃) ₂	-	-
18	C	Cl	-	-
19	C	CH ₂ CH ₃	-	-
20	D	-	-	H
21	D	-	-	CH ₃
22	D	-	-	OCH ₃
23	D	-	-	Cl

Table 2

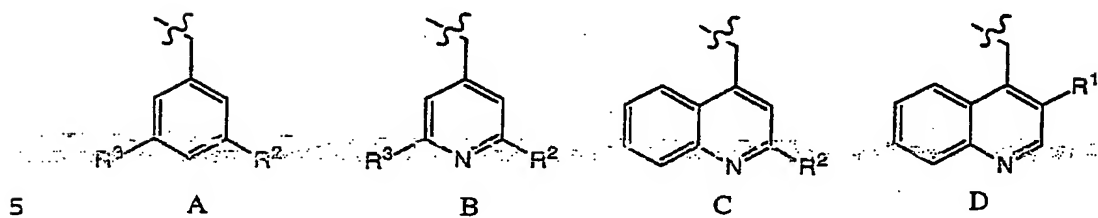
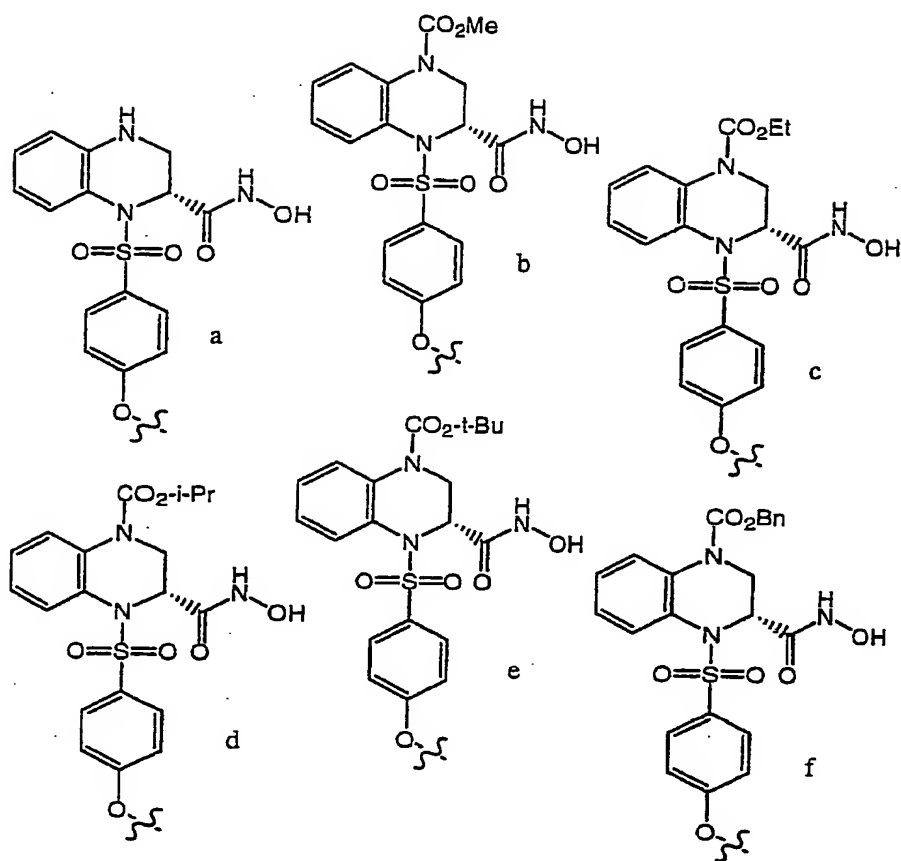


5

Ex #	Core	R ²	R ³	R ¹
1	A	CH ₃	CH ₃	-
2	A	OCH ₃	OCH ₃	-
3	A	CF ₃	CF ₃	-
4	A	OCH ₂ CH ₃	OCH ₂ CH ₃	-
5	A	OCH(CH ₃) ₂	OCH(CH ₃) ₂	-
6	A	Cl	Cl	-
7	A	Br	Br	-
8	B	CH ₃	CH ₃	-

9	B	OCH ₃	OCH ₃	-
10	B	OCH ₂ CH ₃	OCH ₂ CH ₃	-
11	B	OCH(CH ₃) ₂	OCH(CH ₃) ₂	-
12	B	Cl	Cl	-
13	C	H	-	-
14	C	CH ₃	-	-
15	C	OCH ₃	-	-
16	C	OCH ₂ CH ₃	-	-
17	C	OCH(CH ₃) ₂	-	-
18	C	Cl	-	-
19	C	CH ₂ CH ₃	-	-
20	D	-	-	H
21	D	-	-	CH ₃
22	D	-	-	OCH ₃
23	D	-	-	Cl

Table 3



Ex #	Core	R^2	R^3	R^1
1	A	CH_3	CH_3	-
2	A	OCH_3	OCH_3	-
3	A	CF_3	CF_3	-
4	A	OCH_2CH_3	OCH_2CH_3	-
5	A	$\text{OCH}(\text{CH}_3)_2$	$\text{OCH}(\text{CH}_3)_2$	-

6	A	Cl	Cl	-
7	A	Br	Br	-
8	B	CH ₃	CH ₃	-
9	B	OCH ₃	OCH ₃	-
10	B	OCH ₂ CH ₃	OCH ₂ CH ₃	-
11	B	OCH(CH ₃) ₂	OCH(CH ₃) ₂	-
12	B	Cl	Cl	-
13	C	H	-	-
14	C	CH ₃	-	-
15	C	OCH ₃	-	-
16	C	OCH ₂ CH ₃	-	-
17	C	OCH(CH ₃) ₂	-	-
18	C	Cl	-	-
19	C	CH ₂ CH ₃	-	-
20	D	-	-	H
21	D	-	-	CH ₃
22	D	-	-	OCH ₃
23	D	-	-	Cl

Table 4

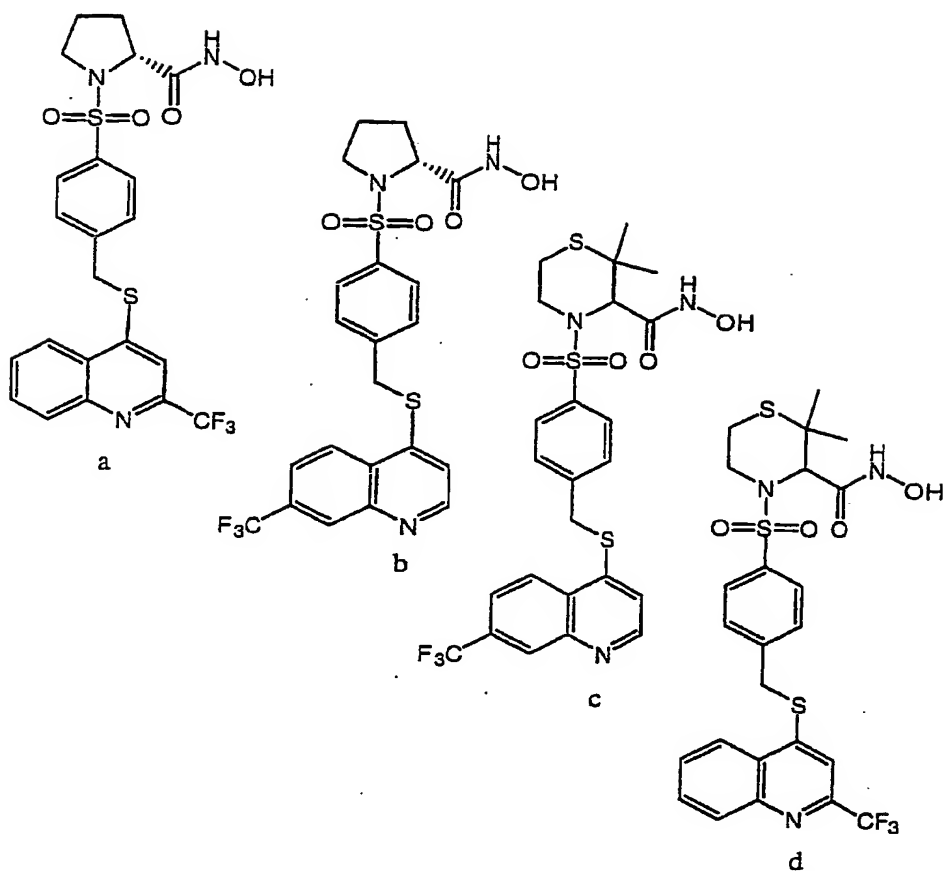
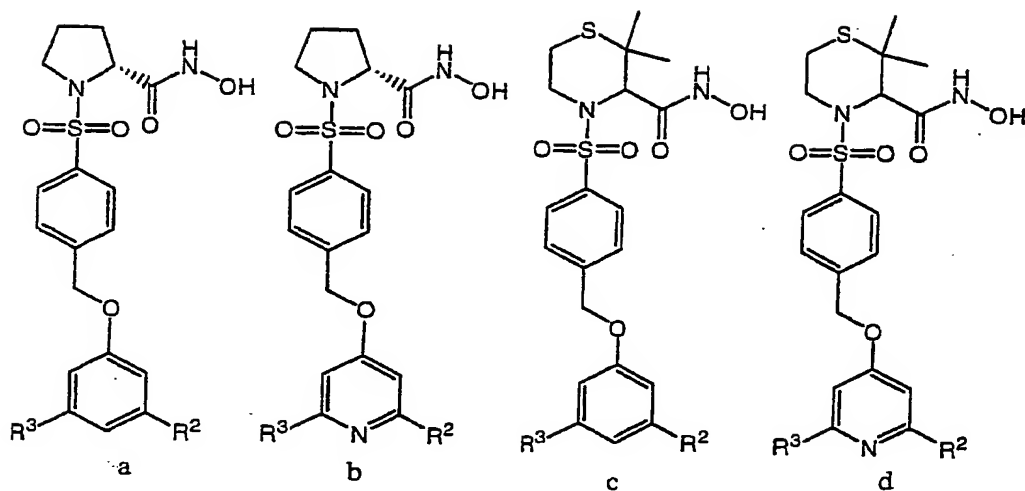
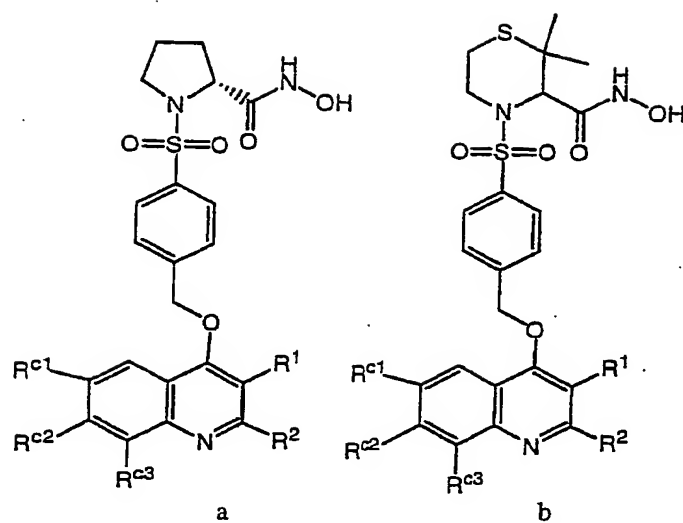


Table 5



Ex #	R^2	R^3
1	CH_3	CH_3
2	OCH_3	OCH_3
3	CF_3	CF_3
4	OCH_2CH_3	OCH_2CH_3
5	$OCH(CH_3)_2$	$OCH(CH_3)_2$
6	Cl	Cl
7	Br	Br
8	CH_3	CH_3
9	OCH_3	OCH_3
10	OCH_2CH_3	OCH_2CH_3
11	$OCH(CH_3)_2$	$OCH(CH_3)_2$

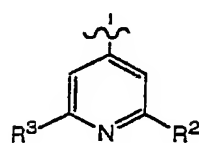
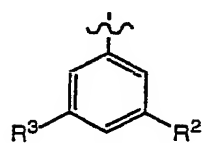
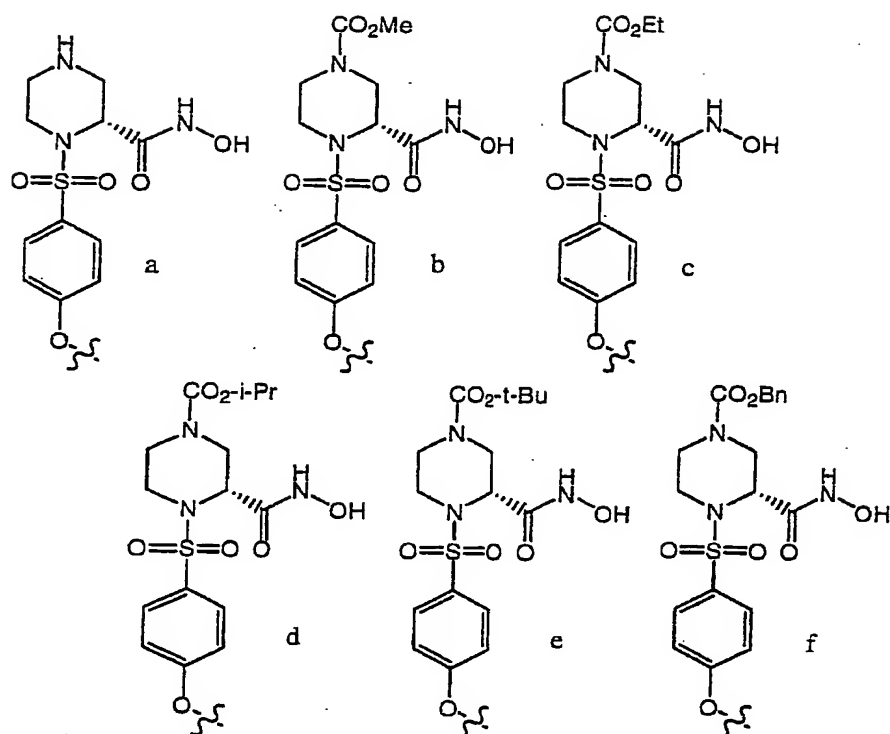
Table 6



Ex #	R^2	R^{c1}	R^{c2}	R^{c3}	R^1
1	CH ₃	H	H	H	H
2	H	H	H	H	H
3	H	H	Cl	H	H
4	H	H	CF ₃	H	H
5	H	OCH ₃	H	H	H
6	CH ₃	H	Cl	H	H
7	CH ₃	F	H	H	H
8	NH ₂	H	H	H	H
9	CF ₃	H	H	CF ₃	H
10	CH ₃	H	OCH ₃	H	H
11	CH ₃	H	H	CF ₃	H
12	CH ₃	H	CF ₃	H	H
13	CH ₃	H	H	CH ₃	H
14	CH ₃	Cl	H	Cl	H
15	CF ₃	H	Cl	H	H
16	H	H	H	CF ₃	H
17	CF ₃	H	Br	H	H
18	CF ₃	H	H	H	H
19	CF ₃	CH ₃	H	H	H

20	H	H	OCH ₃	H	H
21	CF ₃	H	H	OCF ₃	H
22	CF ₃	H	H	Br	H
23	H	CF ₃	H	H	H
24	CH ₂ CH ₃	H	H	H	H
25	CH(CH ₃)	H	H	H	H
26	H	H	H	H	CH ₃
27	H	H	H	H	OCH ₃
28	H	H	H	H	Cl

Table 7

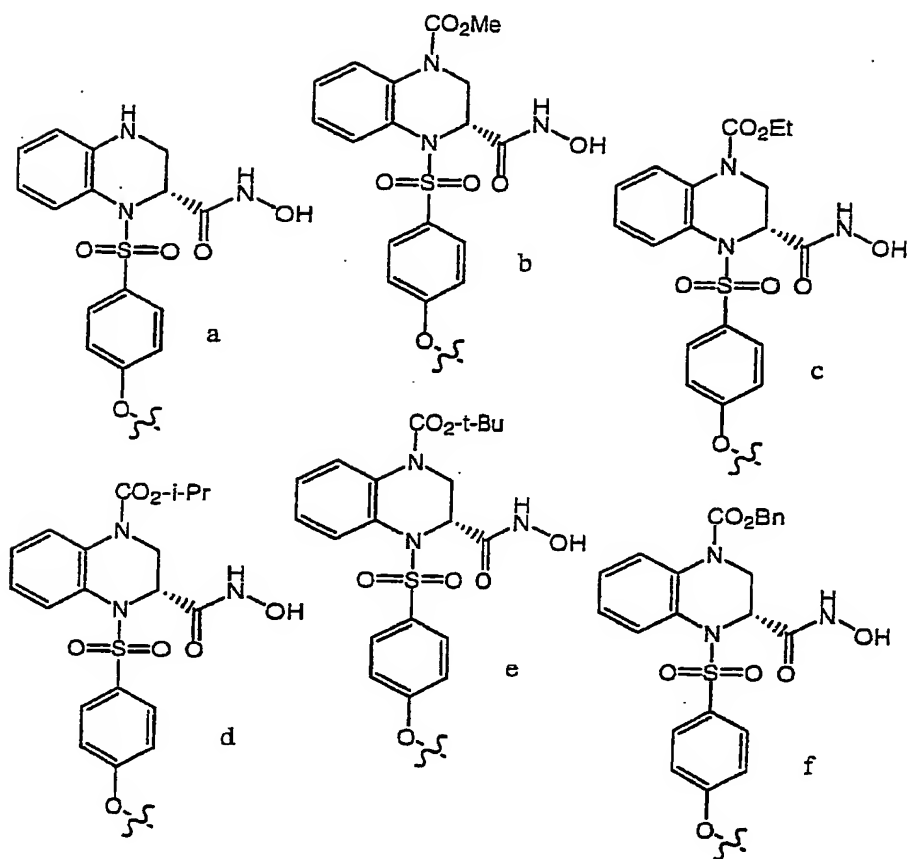


5

Ex #	Core	R ²	R ³
1	A	CH ₃	CH ₃
2	A	OCH ₃	OCH ₃
3	A	CF ₃	CF ₃
4	A	OCH ₂ CH ₃	OCH ₂ CH ₃
5	A	OCH(CH ₃) ₂	OCH(CH ₃) ₂
6	A	Cl	Cl
7	A	Br	Br
8	B	CH ₃	CH ₃
9	B	CF ₃	CF ₃

10	B	C1	C1
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Table 8



Ex #	Core	R ²	R ³
1	A	CH ₃	CH ₃
2	A	OCH ₃	OCH ₃
3	A	CF ₃	CF ₃
4	A	OCH ₂ CH ₃	OCH ₂ CH ₃
5	A	OCH(CH ₃) ₂	OCH(CH ₃) ₂
6	A	Cl	Cl

7	A	Br	Br
8	B	CH ₃	CH ₃
9	B	CF ₃	CF ₃
10	B	Cl	Cl

UTILITY

The compounds of formula I are expected to possess metalloproteinase and TNF inhibitory activity. The compounds provided by this invention should also be useful as standards and reagents in determining the ability of a potential pharmaceutical to inhibit MPs. These would be provided in commercial kits comprising a compound of this invention.

Compounds which inhibit the production or action of TNF and/or MP's are potentially useful for the treatment or prophylaxis of various inflammatory, infectious, immunological or malignant diseases. These include, but are not limited to inflammation, fever, cardiovascular effects, hemorrhage, coagulation and acute phase response, an acute infection, septic shock, haemodynamic shock and sepsis syndrome, post ischaemic reperfusion injury, malaria, Crohn's disease, mycobacterial infection, meningitis, psoriasis, periodontitis, gingivitis, congestive heart failure, fibrotic disease, cachexia, and anorexia, graft rejection, cancer, corneal ulceration or tumor invasion by secondary metastases, autoimmune disease, skin inflammatory diseases, multiple osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, HIV, neurodegenerative diseases, and hyperoxic alveolar injury.

Some compounds of the present invention have been shown to inhibit TNF production in lipopolysaccharide stimulated mice, for example, using the assay for TNF Induction in Mice and in cell assays as described below.

Some compounds of the present invention have been shown to inhibit aggrecanase a key enzyme in cartilage breakdown as determined by the aggrecanase assay described below.

As used herein "µg" denotes microgram, "mg" denotes milligram, "g" denotes gram, "µL" denotes microliter, "mL" denotes milliliter, "L" denotes liter, "nM" denotes nanomolar, "µM" denotes micromolar, "mM" denotes millimolar, "M" denotes molar and "nm" denotes nanometer. "Sigma" stands for the Sigma-Aldrich Corp. of St. Louis, MO.

A compound is considered to be active if it has an IC₅₀ or K_i value of less than about 1 mM for the inhibition of TNF- α production.

5 PBMC ASSAY

Human peripheral blood mononuclear cells (PBMC) were obtained from normal donor blood by leukaphoresis and isolated by Ficoll-Paque density separation. PBMCs were suspended in .5ml RPMI 1640 with no serum at 2 X10⁶ cells/ml in 96 well
10 polystyrene plates. Cells were pre incubated 10 minutes with compound, then stimulated with 1 μ g/ml LPS (Lipopolysaccharide, Salmonella typhimurium) to induce TNF production. After an incubation of 5 hours at 37°C in 95% air, 5% CO₂ environment, culture supernatants were removed and
15 tested by standard sandwich ELISA for TNF production.

TNF Human Whole Blood Assay

Blood is drawn from normal donors into tubes containing 143 USP units of heparin/10ml. 225ul of blood is plated
20 directly into sterile polypropylene tubes. Compounds are diluted in DMSO/serum free media and added to the blood samples so the final concentration of compounds are 50, 10, 5, 1, 0.5, 0.1, and 0.01 μ M. The final concentration of DMSO does not exceed 0.5%. Compounds are preincubated for 15
25 minutes before the addition of 100ng/ml LPS. Plates are incubated for 5 hours in an atmosphere of 5% CO₂ in air. At the end of 5 hours, 750ul of serum free media is added to each tube and the samples are spun at 1200RPM for 10 minutes. The supernatant is collected off the top and assayed for TNF-alpha
30 production by a standard sandwich ELISA. The ability of compounds to inhibit TNF-alpha production by 50% compared to DMSO treated cultures is given by the IC₅₀ value.

TNF Induction In Mice

35 Test compounds are administered to mice either I.P. or P.O. at time zero. Immediately following compound administration, mice receive an I.P. injection of 20 mg of D-galactosamine plus 10 μ g of lipopolysaccharide. One hour

later, animals are anesthetized and bled by cardiac puncture. Blood plasma is evaluated for TNF levels by an ELISA specific for mouse TNF. Administration of representative compounds of the present invention to mice results in a dose-dependent suppression of plasma TNF levels at one hour in the above assay.

MMP Counterscreens

The enzymatic activities of recombinant MMP-1, 2, 3 and 9 were measured at 25 °C with a fluorometric assay (Copeland, R.A.; Lombardo, D.; Giannaras, J. and Decicco, C.P. *Bioorganic Med. Chem. Lett.* 1995, 5, 1947-1952). Final enzyme concentrations in the assay were between 0.05 and 10 nM depending on the enzyme and the potency of the inhibitor tested. The permissive peptide substrate, MCA-Pro-Leu-Gly-Leu-DPA-Ala-Arg-NH₂, was present at a final concentration of 10 uM in all assays. Initial velocities, in the presence or absence of inhibitor, were measured as slopes of the linear portion of the product progress curves. IC50 values were determined by plotting the inhibitor concentration dependence of the fractional velocity for each enzyme, and fitting the data by non-linear least squares methods to the standard isotherm equation (Copeland, R.A. *Enzymes: A practical Introduction to Structure, Mechanism and Data Analysis*, Wiley-VHC, New York, 1996, pp 187-223). All of the hydroxamic acids studied here were assumed to act as competitive inhibitors of the enzyme, binding to the active site Zn atom as previously demonstrated by crystallographic studies of MMP-3 complexed with related hydroxamic acids (Rockwell, A.; Melden, M.; Copeland, R.A.; Hardman, K.; Decicco, C.P. and DeGrado, W.F. *J. Am. Chem. Soc.* 1996, 118, 10337-10338). Based on the assumption of competitive inhibition, the IC50 values were converted to Ki values as previously described.

Dosage and Formulation

The compounds of the present invention can be administered orally using any pharmaceutically acceptable

dosage form known in the art for such administration. The active ingredient can be supplied in solid dosage forms such as dry powders, granules, tablets or capsules, or in liquid dosage forms, such as syrups or aqueous suspensions. The active ingredient can be administered alone, but is generally administered with a pharmaceutical carrier. A valuable treatise with respect to pharmaceutical dosage forms is Remington's Pharmaceutical Sciences, Mack Publishing.

The compounds of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. Likewise, they may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compound desired can be employed as an antiinflammatory and antiarthritic agent.

The compounds of this invention can be administered by any means that produces contact of the active agent with the agent's site of action in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. An ordinarily skilled

physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per day, and most preferably between about 1.0 to 20 mg/kg/day. For a normal male adult human of approximately 70 kg of body weight, this translates into a dosage of 70 to 1400 mg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Advantageously, compounds of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

The compounds for the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

In the methods of the present invention, the compounds herein described in detail can form the active ingredient, and are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as carrier materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral

administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like.

Moreover, when desired or necessary, suitable binders,

- 5 lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate,
- 10 carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar,
- 15 bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a

20 variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer,

25 polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled

30 release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacylates, and crosslinked or amphipathic block

35 copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these

pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parenterally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field. Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

Capsules are prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 100 milligrams of cellulose and 10 milligrams of magnesium stearate.

A large number of unit capsules may also prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Syrup

		<u>Wt. %</u>
15	Active Ingredient	10
	Liquid Sugar	50
	Sorbitol	20
	Glycerine	5
	Flavor, Colorant and	as required
20	Preservative	
	Water	as required

The final volume is brought up to 100% by the addition of distilled water.

Aqueous Suspension

		<u>Wt. %</u>
	Active Ingredient	10
	Sodium Saccharin	0.01
30	Keltrol® (Food Grade Xanthan Gum)	0.2
	Liquid Sugar	5
	Flavor, Colorant and	as required
	Preservative	
35	Water	as required

Xanthan gum is slowly added into distilled water before adding the active ingredient and the rest of the formulation ingredients. The final suspension is passed through a homogenizer to assure the elegance of the final products.

Resuspendable Powder

		<u>Wt. %</u>
45	Active Ingredient	50.0
	Lactose	35.0
	Sugar	10.0
	Acacia	4.7
	Sodium Carboxymethylcellulose	0.3
50	Each ingredient is finely pulverized and then uniformly mixed together. Alternatively, the powder	

can be prepared as a suspension and then spray dried.

Semi-Solid Gel

5		<u>Wt. %</u>
	Active Ingredient	10
	Sodium Saccharin	0.02
	Gelatin	2
	Flavor, Colorant and	as required
10	Preservative	
	Water	as required

15 Gelatin is prepared in hot water. The finely pulverized active ingredient is suspended in the gelatin solution and then the rest of the ingredients are mixed in. The suspension is filled into a suitable packaging container and cooled down to form the gel.

Semi-Solid Paste

20		<u>Wt. %</u>
	Active Ingredient	10
	Gelcarin® (Carrageenin gum)	1
	Sodium Saccharin	0.01
25	Gelatin	2
	Flavor, Colorant and	as required
	Preservative	
	Water	as required

30 Gelcarin® is dissolved in hot water (around 80°C) and then the fine-powder active ingredient is suspended in this solution. Sodium saccharin and the rest of the formulation ingredients are added to the suspension while it is still warm. The suspension is homogenized and then filled into suitable containers.

Emulsifiable Paste

40		<u>Wt. %</u>
	Active Ingredient	30
	Tween® 80 and Span® 80	6
	Keltrol®	0.5
	Mineral Oil	63.5

45 All the ingredients are carefully mixed together to make a homogenous paste.

Soft Gelatin Capsules

50 A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin

to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

5 Tablets may be prepared by conventional procedures so that the dosage unit is 500 milligrams of active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose and 10 milligrams of magnesium stearate.

10 A large number of tablets may also be prepared by conventional procedures so that the dosage unit was 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings
15 may be applied to increase palatability or delay absorption.

Injectable

20 A parenteral composition suitable for administration by injection is prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The solution is made isotonic with sodium chloride and sterilized.

Suspension

25 An aqueous suspension is prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

30 The compounds of the present invention may be administered in combination with a second therapeutic agent, especially non-steroidal anti-inflammatory drugs (NSAID's). The compound of Formula I and such second therapeutic agent can be administered separately or as a physical combination in a single dosage unit, in any dosage form and by various routes
35 of administration, as described above.

The compound of Formula I may be formulated together with the second therapeutic agent in a single dosage unit (that is, combined together in one capsule, tablet, powder, or liquid,

etc.). When the compound of Formula I and the second therapeutic agent are not formulated together in a single dosage unit, the compound of Formula I and the second therapeutic agent may be administered essentially at the same time, or in any order; for example the compound of Formula I may be administered first, followed by administration of the second agent. When not administered at the same time, preferably the administration of the compound of Formula I and the second therapeutic agent occurs less than about one hour apart, more preferably less than about 5 to 30 minutes apart.

Preferably the route of administration of the compound of Formula I is oral. Although it is preferable that the compound of Formula I and the second therapeutic agent are both administered by the same route (that is, for example, both orally), if desired, they may each be administered by different routes and in different dosage forms (that is, for example, one component of the combination product may be administered orally, and another component may be administered intravenously).

The dosage of the compound of Formula I when administered alone or in combination with a second therapeutic agent may vary depending upon various factors such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration, the age, health and weight of the recipient, the nature and extent of the symptoms, the kind of concurrent treatment, the frequency of treatment, and the effect desired, as described above.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients,

but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a sustained-release material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

The present invention also includes pharmaceutical kits useful, for example, in the treatment or prevention of osteoarthritis or rheumatoid arthritis, which comprise one or more containers containing a pharmaceutical composition

comprising a therapeutically effective amount of a compound of Formula I. Such kits may further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines

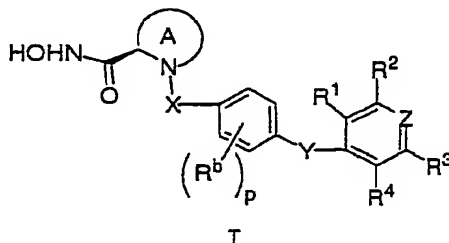
for administration, and/or guidelines for mixing the components, may also be included in the kit.

5 In the present disclosure it should be understood that the specified materials and conditions are important in practicing the invention but that unspecified materials and conditions are not excluded so long as they do not prevent the benefits of the invention from being realized.

10 Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

WHAT IS CLAIMED AS NEW AND DESIRED TO BE SECURED BY
LETTER PATENT OF UNITED STATES IS:

1. A compound of formula I:



or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

10

ring A is a 5-8 membered heterocyclic ring containing 0-1 additional heteroatoms selected from the group: O, NH, S, SO, and SO₂, and substituted with 0-3 R^a;

15 R^a, at each occurrence, is independently selected from the group: =O, CH₃, CH₂CH₃, CF₃, Cl, F, OH, OCH₃, and OCF₃;

R^b, at each occurrence, is independently F or CH₃;

20 X is selected from the group: CH₂, C(O), C(O)O, C(O)NH, S(O), S(O)₂, S(O)NH, and S(O)₂NH;

Y is selected from the group: (CH₂)_n, OCH₂, CH₂O, OCH(CH₃), CH(CH₃)O, OC(CH₃)₂, C(CH₃)₂O, OCF₂, CF₂O, S(O)_pCH₂,

25 CH₂S(O)_p, NH, NHCH₂, and CH₂NH;

Z is CH or N;

30 R¹ is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R² is selected from the group: F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R^3 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 ,
 $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

provided that when Z is N, R^2 and R^3 are other than F, Br, or
 5 I;

R^4 is H;

alternatively, R^3 and R^4 are taken together with the carbon
 10 atoms to which they are attached to form a 5-6 membered
 aromatic ring containing 0-2 heteroatoms selected from
 the group: O, S, NH, and N and substituted with 0-2 R^c ;

R^c is selected from the group: H, F, Cl, Br, I, NO_2 , CH_3 ,
 15 CH_2CH_3 , $CH(CH_3)_2$, OCH_3 , OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

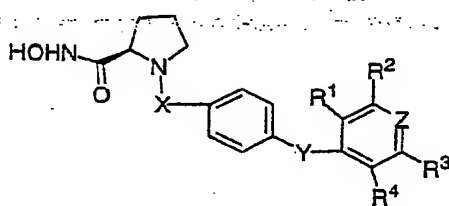
when R^3 and R^4 are taken together, then R^2 is selected from
 the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 , $CH(CH_3)_2$, OCH_3 ,
 20 OCH_2CH_3 , $OCH(CH_3)_2$, CF_3 , and OCF_3 ;

n is selected from the group: 1, 2, and 3; and,

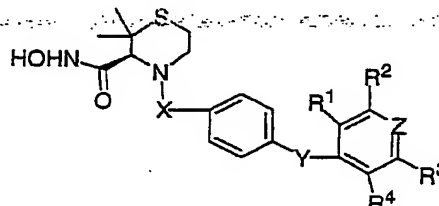
p is selected from the group: 0, 1, and 2.

25

2. A compound according to Claim 1, wherein the compound
 is of formula Ia or Ib:



Ia



Ib

wherein, X is selected from the group: CH_2 , $C(O)$, $C(O)O$,
 $C(O)NH$, $S(O)$, $S(O)_2$, $S(O)NH$, and $S(O)_2NH$;

Y is selected from the group: CH_2 , $(\text{CH}_2)_2$, OCH_2 , CH_2O , NH , NHCH_2 , and CH_2NH ;

5 Z is CH or N;

R^1 is selected from the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;

10 R^2 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;

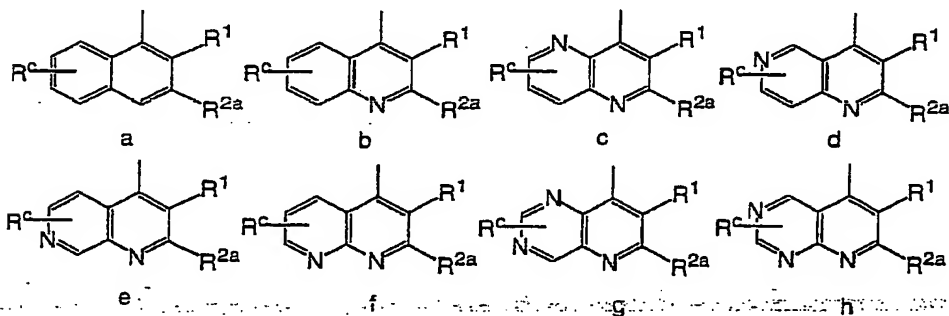
R^3 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;

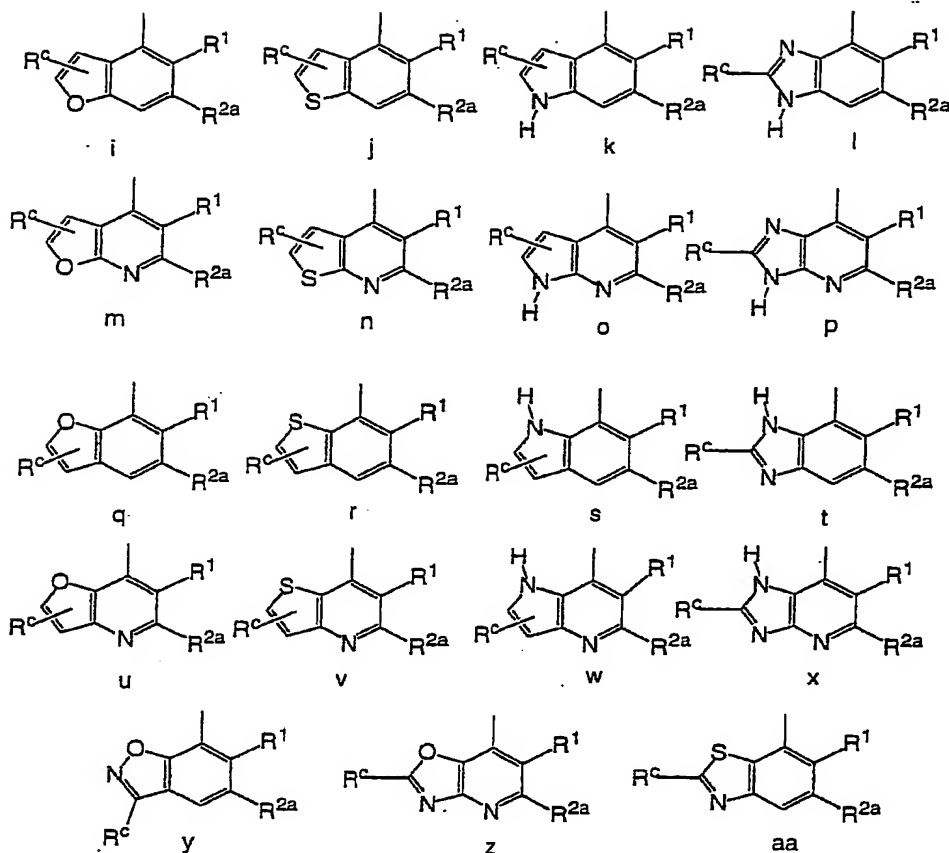
15

R^4 is H;

alternatively, R^3 and R^4 are taken together with the aromatic ring to which they are attached to form an aromatic ring selected from a-aa:

20





5 R^c is selected from the group: H, F, Cl, Br, I, NO₂, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃; and,

R^{2a} is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃.

3. A compound according to Claim 1, wherein the compound is selected from:

15 (S)-4-[[4-[(3,5-dimethylphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;

20 (S)-4-[[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;

- (S)-4-[[4-[(3,5-ditrifluoromethylphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 5 (S)-4-[[4-[(3,5-dibromophenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(3,5-diethoxyphenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 10 (S)-4-[[4-[(3,5-dichlorophenyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 15 (S)-4-[[4-[(2,6-dimethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-4-[[4-[(2,6-diethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 20 (S)-4-[[4-[(2,6-ditrifluoromethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- 25 (S)-4-[[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-3-thiomorpholinecarboxamide;
- (S)-N-hydroxy-2,2-dimethyl-4-[[4-(4-quinolinylmethoxy)phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 30 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(2-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 35 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(2-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 40 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(2-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 45 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(2-ethoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 50 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(2-trifluoromethyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 55

- 1-[[4-[(3,5-dimethylphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 5 1-[[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(3,5-ditrifluoromethylphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 10 1-[[4-[(3,5-dibromophenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(3,5-diethoxyphenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 15 1-[[4-[(3,5-dichlorophenyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 20 1-[[4-[(2,6-dimethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-[(2,6-diethoxy-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 25 1-[[4-[(2,6-ditrifluoromethyl-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 30 1-[[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[4-(4-quinolinylmethoxy)phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 35 1-[[[4-(2-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 40 1-[[[4-(2-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[[4-(2-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 45 1-[[4-(2-ethoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 1-[[[4-(2-trifluoromethyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;
- 50 (S)-N-hydroxy-2,2-dimethyl-4-[[[4-(3-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;
- 55

(S) -N-hydroxy-2,2-dimethyl-4-[[[4-(3-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;

(S) -N-hydroxy-2,2-dimethyl-4-[[[4-(3-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-3-thiomorpholinecarboxamide;

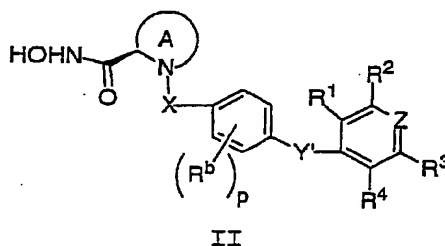
1-[[[4-(3-chloro-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;

1-[[[4-(3-methyl-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide; and,

1-[[[4-(3-methoxy-4-quinolinyl)methoxy]phenyl]sulfonyl]-D-proline-N-hydroxyamide;

or a pharmaceutically acceptable salt form thereof.

4. A compound of formula II:



or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

ring A is a 5-8 membered heterocyclic ring containing 0-1

additional heteroatoms selected from the group: O, NH, S, SO, and SO₂, and substituted with 0-3 R^a;

R^a, at each occurrence, is independently selected from the group: =O, CH₃, CH₂CH₃, CF₃, Cl, F, OH, OCH₃, and OCF₃;

R^b, at each occurrence, is independently F or CH₃;

X is selected from the group: CH₂, C(O), C(O)O, C(O)NH, S(O), S(O)₂, S(O)NH, and S(O)₂NH;

Y' is S or O;

Z is CH or N;

5

R¹ is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

10 R² is selected from the group: F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

R³ is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

15 provided that when Z is N, R² and R³ are other than F, Br, or I;

R⁴ is H;

20 alternatively, R³ and R⁴ are taken together with the carbon atoms to which they are attached to form a 5-6 membered aromatic ring containing 0-2 heteroatoms selected from the group: O, S, NH, and N and substituted with 0-1 R^c;

25 R^c is selected from the group: H, F, Cl, Br, I, NO₂, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

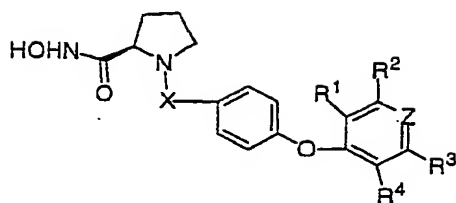
30 when R³ and R⁴ are taken together, then R² is selected from the group: H, F, Cl, Br, I, CH₃, CH₂CH₃, CH(CH₃)₂, OCH₃, OCH₂CH₃, OCH(CH₃)₂, CF₃, and OCF₃;

n is selected from 1, 2, and 3; and,

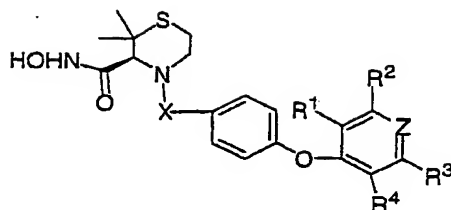
p is selected from 0, 1, and 2.

35

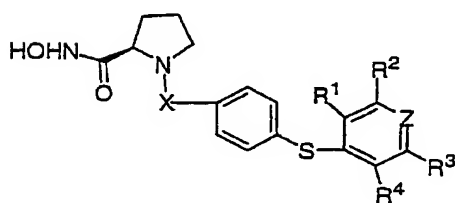
5. A compound according to Claim 4, wherein the compound is of formula IIa, IIb, IIc or IId:



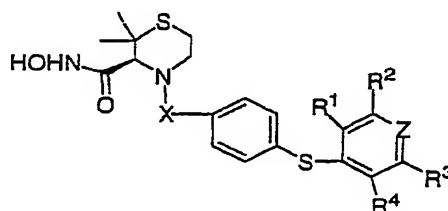
IIa



IIb



IIc



IIId

wherein, X is selected from the group: CH_2 , $\text{C}(\text{O})$, $\text{C}(\text{O})\text{O}$,
 $\text{C}(\text{O})\text{NH}$, $\text{S}(\text{O})$, $\text{S}(\text{O})_2$, $\text{S}(\text{O})\text{NH}$, and $\text{S}(\text{O})_2\text{NH}$;

Z is CH or N;

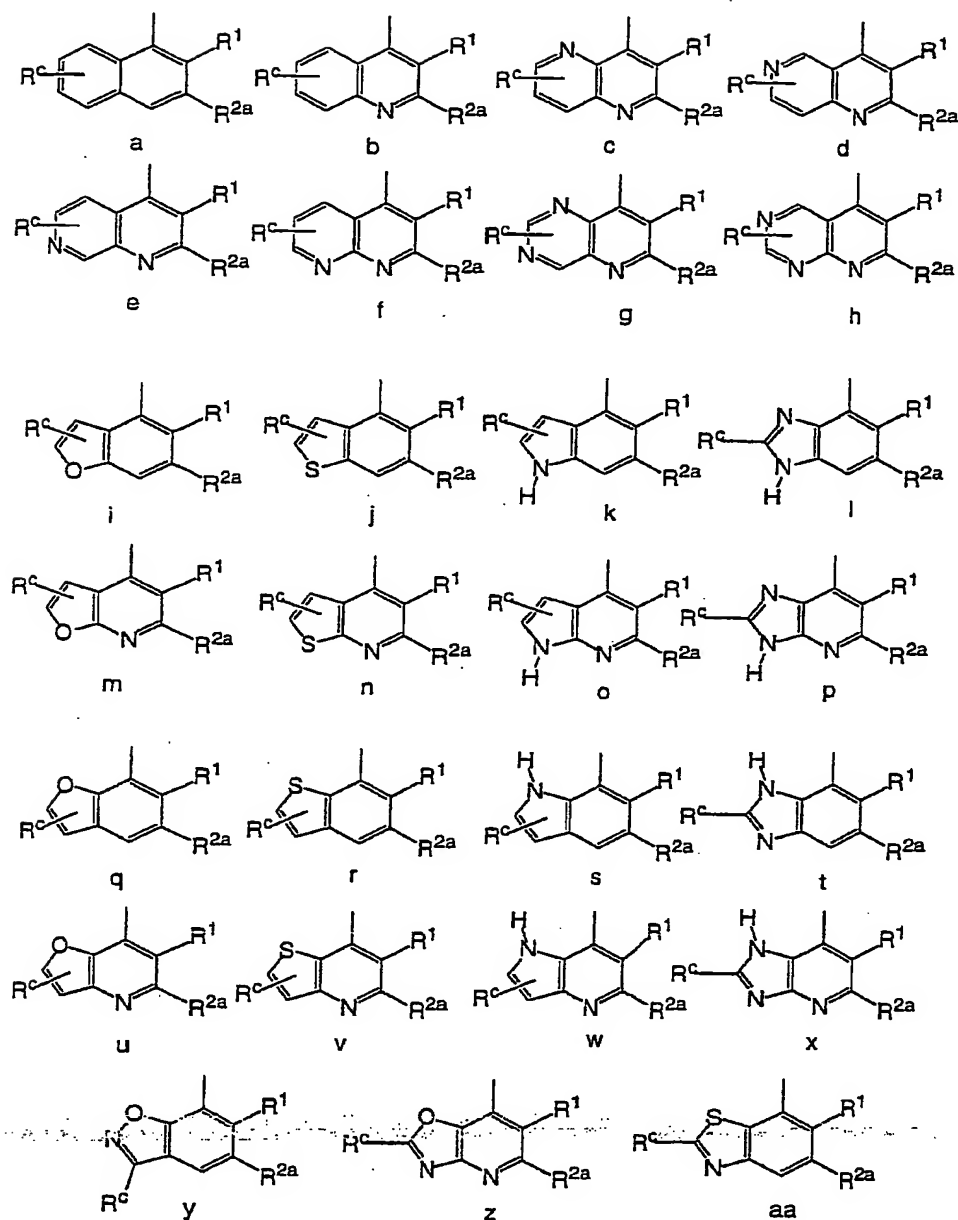
R^1 is H or F;

R^2 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 ,
 $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;

R^3 is selected from the group: F, Cl, Br, I, CH_3 , CH_2CH_3 ,
 $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ;

R^4 is H;

alternatively, R^3 and R^4 are taken together with the aromatic
 ring to which they are attached to form an aromatic ring
 selected from a-aa:



R^c is selected from the group: H, F, Cl, Br, I, NO_2 , CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 ; and,

R^{2a} is selected from the group: H, F, Cl, Br, I, CH_3 , CH_2CH_3 , $\text{CH}(\text{CH}_3)_2$, OCH_3 , OCH_2CH_3 , $\text{OCH}(\text{CH}_3)_2$, CF_3 , and OCF_3 .

6. A pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, or 5 or a pharmaceutically acceptable salt form thereof.

7. A method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, or 5 or a pharmaceutically acceptable salt form thereof.

8. A method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, or 5 or a pharmaceutically acceptable salt form thereof.

9. A method of reducing levels of TNF in patients without inhibiting MMPs, comprising: MMP-1, MMP-2, and MMP-9, and reduce the potential of side effects mediated by these enzymes comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, or 5 or a pharmaceutically acceptable salt form thereof.

10. A method of treating a condition or disease wherein the disease or condition is referred to as rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, multiple sclerosis, neurodegenerative diseases, psoriasis, autoimmune disease, Crohn's disease, inflammatory bowel disease, or HIV infection in a mammal, comprising:

administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, or 5 or a pharmaceutically acceptable salt form thereof.

5

11. A method of treating a condition or disease wherein the disease or condition is referred to as fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, solid tumor growth and tumor invasion by secondary metastases, or neovascular glaucoma, in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, or 5 or a pharmaceutically acceptable salt form thereof.

10

15

12. A compound of Claim 1, 2, 3, 4, or 5 for use in therapy.

20

13. The use of a compound of Claim 1, 2, 3, 4, or 5 for the manufacture of a medicament for the treatment of a disease related to metalloproteases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/10357

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D417/12 C07D401/12 C07D279/12 C07D207/16 A61K31/54
A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	WO 98 50348 A (AGOURON PHARMA ; BENDER STEVEN L (US)) 12 November 1998 see claims; examples	1, 4, 6-13
X, P	WO 98 34918 A (MCCLURE KIM FRANCIS ; PFIZER (US)) 13 August 1998 see the whole document	1, 4, 6-13
X	WO 97 20824 A (AGOURON PHARMA ; ZOOK SCOTT E (US); DAGNINO RAYMOND JR (US); DEASON) 12 June 1997 cited in the application see claims; examples	1, 4, 6-13
X	WO 98 08825 A (PROCTER & GAMBLE) 5 March 1998 see claims; examples	1, 4, 6-13

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 July 1999

Date of mailing of the international search report

12/07/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Bosma, P

INTERNATIONAL SEARCH REPORT

Intern: 31 Application No
PCT/US 99/10357

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 98 08815 A (PROCTER & GAMBLE) 5 March 1998 see claims	1,4,6-13
A	WO 97 18194 A (HOECHST AG) 22 May 1997 see claims 1,6-9; table 1	1,4,6-13

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/10357

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim(s) 7-11
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/10357

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